

AMENDMENTS TO THE SPECIFICATION

Please replace paragraph 7 beginning at line 19 on page 7 with the following amended paragraph:

Fig. 4A are 4 shows electroencephalograph (EEG) recordings displaying the kainate induced seizure damage in the hippocampus and the neuroprotective effect on status epilepticus (SE) in AAVNMDAR1 treated animals;

Please replace paragraph 4 beginning at line 21 on page 39 with the following amended paragraph:

In another preferred embodiment, the neurological disorder is epilepsy. In the case of epilepsy, there are both rat and monkey models in which effective therapies are predictive of therapeutic efficacy in humans. For example, rats which exhibit audiogenic seizures are commercially available. Example 4 demonstrates in detail the neuroprotective effect of the AAVNMDAR1 vaccine against seizures in the kainate epilepsy model. Antigen, antibodies or antibody portions of the invention can be introduced into the systemic circulation of these animals and seizures initiated. The neuroprotective capacity of the vaccine was determined by monitoring the onset, or decrease in seizure occurrence by EEG. Fig. 4A 4 shows the reduction in epileptic seizures in animals vaccinated with the AAVNMDAR1 vaccine of the invention.

Please replace paragraph 2 beginning at line 12 on page 59 with the following amended paragraph:

Fig. 4A 4 shows that kainate-induced seizure activity was evident shortly after drug administration as shown by EEG recordings. The first signs of electrographic seizure activity was observed within 10 minutes following drug administration in control animals, with 13 out of 17 naïve and 6 of the 8 AAVlac animals developing facial and forearm clonus and proceeding to status epilepticus (SE). In contrast, only 2 out of the 9 AAVNMDAR1-vaccinated animals

developed seizures and SE (Table 1). The remaining 7 AAVNMDAR1 rats showed neither EEG changes nor any behavioural changes following kainate ($p=0.007$, Chi Square analysis with expected SE frequency of 68% reduced to 22% in the NMDAR1-immunized group). In those rats which exhibited SE, seizures were terminated with an anticonvulsant dose of sodium pentobarbital (30 mg/kg i.p.) after 45 minutes. Animals that did not develop seizures also received pentobarbital (30 mg/kg i.p.).

Please replace paragraph 2 beginning at line 8 on page 60 with the following amended paragraph:

One AAVNMDAR1-vaccinated rat that developed SE also showed extensive clusterin and TUNEL staining. Of interest, the second animal that developed SE showed no TUNEL signal or clusterin immunofluorescence. The EEG recordings shown in (Fig. 4A 4) correspond to the brains analyzed. Kainate-induced seizures were also elicited in AAVGAD65-vaccinated animals and TUNEL and clusterin labelling confirmed extensive neuronal damage in the hippocampus. Scale 200 μ m.

Please replace the paragraph beginning at line 11 on page 67 and ending at line 2 on page 68 with the following replacement paragraph:

The results from these studies are described below. Confocal images of non-treated control cells were taken. Confocal images were taken showing intracellular Ca^{2+} imaging of cultured mesencephalic neurons and AAVNMDAR1 IgG innumoreactivity in mesencephalic and rat hippocampal neurons. -NMDAR1 IgG-treated mesencephalic cells preloaded with the Ca^{2+} indicator Oregon Green 488 BAPTA-1 (2 μ M) showed low level fluorescence. Cells were preincubated with 50 μ g/ml IgG for 16 h prior to indicator loading. In response to a 100 μ M NMDA+3 pM glycine challenge, the increase in fluorescent signal found in non-treated control

and AAVlac IgG-treated cells was significantly attenuated in AAVNMDAR1 IgG-treated cells. Images are pseudocoloured according to fluorescent intensity, with transition from red to yellow representing basal Ca^{2+} levels to higher Ca^{2+} concentrations (data not shown). Fig. 8 shows ratio of the changes in fluorescent intensity relative to basal levels showed a significant difference between AAVlac and AAVNMDAR1 IgG-treated cells. Each bar represents the mean \pm SEM, n=10 (*p=0.0012, Student's t-test). Anti-rat IgG immunocytochemistry showed only purified AAVNMDAR1 IgG bound to mesencephalic cells and not AAVlac IgG which exhibited basal immunoreactivity similar to non-treated cells. Using the IgG fractions to perform immunohistochemistry on brain sections, as shown in hippocampal hilar neurons, the AAVNMDAR1 IgG showed a pattern of immunoreactivity similar to that found with a commercial NMDAR1 polyclonal antibody, while AAVlac IgG showed only low level background immunoreactivity.